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Aortic valve disease : novel imaging insights from diagnosis to therapy

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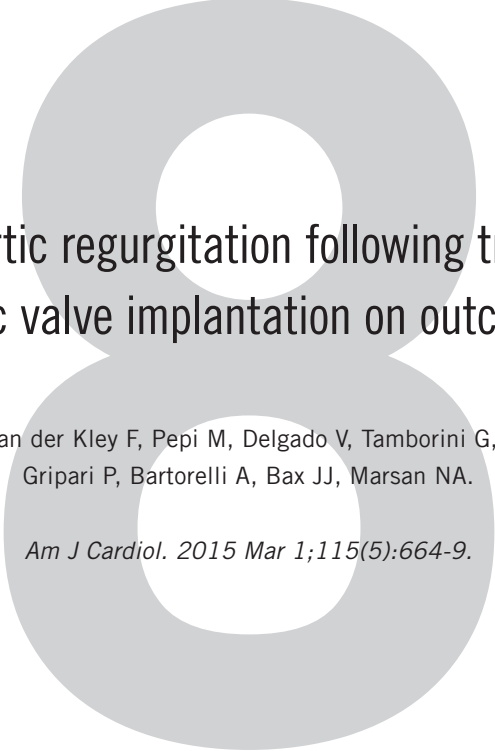


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Effect of aortic regurgitation following transcatheter aortic valve implantation on outcomes

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Effect of Aortic Regurgitation Following Transcatheter Aortic Valve Implantation on Outcomes



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The prognosis of aortic regurgitation (AR) after transcatheter aortic valve implantation (TAVI) and the changes in AR grade over time remain unclear. This study evaluated the midterm survival associated with AR after TAVI and examined the evolution of AR over time and its effect on cardiac performance. Successful TAVI was performed in 314 patients (age 81 ± 7 years, 36% men). Serial transthoracic echocardiography and clinical assessment were available in 175 patients who survived >12 months. AR was assessed in terms of overall, paravalvular, and intravalvular severity. Significant post-TAVI AR (grade ≥ 2) was observed in 82 patients (26%), and these patients showed a trend toward reduced survival at 1- (93% vs 91%) and 2-year (89% vs 74%, log-rank $p = 0.063$) follow-up. Of the 175 patients who survived >12 months, grade ≥ 2 overall, paravalvular, and intravalvular AR were noted in 47 (27%), 32 (18%), and 8 patients (5%), respectively. Significant overall and paravalvular AR appeared to improve over time, particularly during the first 6 months ($p < 0.05$), whereas intravalvular AR remained unchanged. Although improvements in the echocardiographic parameters were similar among patients with and without significant AR, patients who remained with grade ≥ 2 AR at 6 months had significantly worse survival than their counterparts at 2 years (80% vs 94%, log-rank $p = 0.032$). In conclusion, significant overall and paravalvular AR after TAVI appeared to improve over time. Although improvements in the echocardiographic parameters were similar, patients with grade ≥ 2 AR, both immediately after TAVI and at 6 months, were associated with worse survival. © 2015 Elsevier Inc. All rights reserved. (Am J Cardiol 2015;115:664–669)

Transcatheter aortic valve implantation (TAVI) is an established alternative therapy for patients with symptomatic severe aortic stenosis (AS) who are deemed to have high risk or contraindications for conventional surgery.¹ Although advances in technical devices and proper patient selection have significantly improved TAVI results,^{2,3} aortic regurgitation (AR) remains a common finding after TAVI. Moreover, significant AR after TAVI has been associated with an increase in in-hospital mortality and less favorable clinical outcomes.^{2,4–6} However, the changes in post-TAVI AR during follow-up and its effect on long-term clinical outcomes remain to be clarified. Therefore, the aim of the study was twofold: first, to evaluate the midterm survival associated with AR after TAVI; and second, to examine the evolution of AR over time and its effect on cardiac performance and outcomes at mid- and long-term follow-up.

Methods

Patients with symptomatic severe AS who underwent successful TAVI at Leiden University Medical Center, Leiden, the Netherlands, and Centro Cardiologico Monzino, IRCCS, Milan, Italy, were included. All patients had severe AS, defined as an aortic valve area $< 1 \text{ cm}^2$ or $< 0.6 \text{ cm}^2/\text{m}^2$, and were considered at high risk or had contraindications for conventional valve surgery. All consecutive patients with successful TAVI procedures who survived the index hospitalization, from November 2007 to March 2011, were included. Patients with bicuspid aortic valves or previous aortic or mitral prostheses were excluded. For the subsequent analysis, which aimed at evaluating the changes over time of AR after TAVI and its effect on cardiac hemodynamics and clinical outcomes, patients with a follow-up duration of at least 12 months after implantation were included. According to the institutional protocols, all patients underwent clinical and echocardiographic evaluation at baseline, after the procedure (before hospital discharge), at 6 months, and then annually. Clinical and echocardiographic data were prospectively recorded and subsequently analyzed. All patients received either the 23- or 26-mm balloon-expandable Edwards-SAPIEN valves (Edwards Lifesciences, Inc., Irvine, California) depending on the diameter of the aortic annulus.⁷ Only 2 patients received the 29-mm valve. The device was delivered through either the transfemoral or transapical approach (in patients with unsuitable aortoiliac anatomy).⁸

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See page 669 for disclosure information.

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Table 1
Baseline patient characteristics

Variable		Patients (n=314)
Age (years)		81.2±6.5
Men		114 (36%)
Body surface area (m ²)		1.72±0.20
Logistic EuroSCORE (%)		20.5±11.4
Systolic blood pressure (mmHg)		129±20
Diastolic blood pressure (mmHg)		71±10
NYHA functional class	II	80 (26%)
	III	172 (55%)
	IV	62 (20%)
Previous myocardial infarction		62 (20%)
Previous coronary bypass surgery		63 (20%)
Previous percutaneous coronary intervention		80 (26%)
Peripheral vascular disease		126 (40%)
Hypertension*		255 (81%)
Hypercholesterolaemia*		165 (53%)
Diabetes mellitus		88 (28%)
Hemoglobin (g/dL)		12.0±1.6
Heart rhythm	Sinus	238 (77%)
	Atrial fibrillation	53 (17%)
	Paced	23 (7%)
Frailty		75 (24%)
Aortic valve area (cm ²)		0.68±0.17
Mean transaortic gradient (mmHg)		48±16
Left ventricular ejection fraction (%)		54.8±12.5
Approach	Transfemoral	171 (55%)
	Transapical	143 (46%)

Continuous data are presented as mean±SD and categorical data as n (%).

* Hypertension: history of high blood pressure and/or on antihypertensive treatment. Hypercholesterolemia: history of hypercholesterolemia and/or on statin therapy.

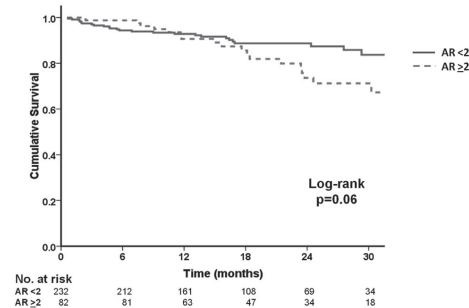


Figure 1. Survival Kaplan-Meier curves for patients with post-TAVI AR grade ≥ 2 or < 2 before hospital discharge.

Standard 2-dimensional, color and Doppler transthoracic echocardiography was performed in all patients at baseline, after the procedure (before hospital discharge), at 6 months, and annually, using a commercially available ultrasound system (Vivid-7; General Electric, Horten, Norway). All images were digitally stored for offline analysis (EchoPAC, version 110.0.0; GE-Vingmed, Horten, Norway). The left ventricular (LV) outflow tract, aortic annulus diameters, and transaortic gradient were measured, as recommended, and

aortic valve area was calculated using the continuity equation.^{9,10} Standard LV dimensions were obtained, and LV mass index was calculated according to Devereux et al and corrected for body surface area.^{9,11} Using the biplane Simpson's method, LV end-diastolic and end-systolic volumes and maximal left atrial (LA) volumes were measured, and LV ejection fraction was derived.⁹

The presence of AR of the native aortic valve at baseline was assessed using color Doppler recordings as recommended.¹² To evaluate the presence and severity of AR after TAVI, a combination of the qualitative and semiquantitative parameters was used according to the current guidelines, after optimizing gain and Nyquist scale (50 to 60 cm/s).^{13,14} For intravalvular AR, similar method for assessment of native valvular regurgitation (in terms of ratio of the regurgitant jet to the LV outflow tract width) was applied: $< 25\%$ mild, 26% to 64% moderate, and $> 65\%$ severe.^{13,14} For paravalvular AR, the proportion of the circumference of the prosthesis occupied by the jet allowed semiquantitative assessment of its severity as described: $< 10\%$ mild, 10% to 20% moderate, and $> 20\%$ severe.^{13,15} Finally, the assessment of overall AR severity involved integration of all these parameters and was graded as follows: grade 0 (none), grade 1 (mild) when either intravalvular or paravalvular AR was mild, grade 2 (mild to moderate) when both mild intravalvular and mild paravalvular AR were present or when either intravalvular or paravalvular AR was moderate, grade 3 (moderate to severe) when both moderate intravalvular and moderate paravalvular AR were present, and grade 4 (severe) when either intravalvular or paravalvular AR was severe. Significant AR after TAVI was defined as overall AR grade ≥ 2 .

Before hospital discharge and at 6 months, and annually, clinical evaluation was performed, including the classification of heart failure symptoms according to the New York Heart Association functional class. All adverse events¹⁵ and mortality were recorded.

Continuous variables are presented as mean $\pm$ SD. Categorical variables are presented as percentages. Preprocedural and follow-up data were compared between patients with (AR grade ≥ 2) and without significant AR (AR grade < 2). Unpaired Student *t* test, chi-square test, or Fisher's exact test was used to compare continuous or categorical variables, as appropriate. In addition, the survival rates are presented as Kaplan-Meier curves, and the log-rank test was used for comparisons between patients with and without significant AR. To examine the changes in AR severity over time, the nonparametric Friedman test for repeated measures was used, followed by post hoc analyses for significant results using a paired Wilcoxon analysis. Finally, repeated-measures analysis of variance was used to evaluate the repeated echocardiographic variables (at different time points), followed by post hoc analyses for significant results using Bonferroni correction. A 2-tailed probability value of < 0.05 was considered statistically significant. All statistical analyses were conducted using SPSS for Windows, version 16 (SPSS Inc., Chicago, Illinois).

Results

Baseline clinical characteristics of the 314 patients (age 81 ± 7 years, 36% men) are summarized (Table 1). Post-TAVI AR (before hospital discharge) was observed in 237

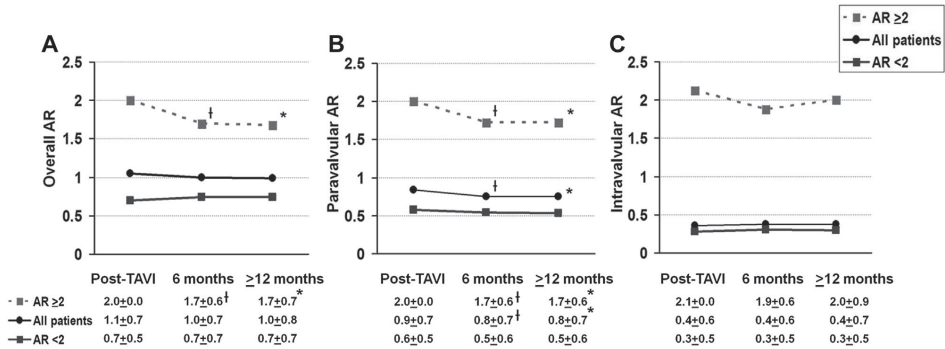


Figure 2. Comparison of changes in the overall (A), paravalvular (B), and intravalvular (C) AR severity after TAVI in the entire population, in patients with (grade ≥ 2) and without (grade < 2) significant post-TAVI AR. AR severity at the corresponding time point was given as mean $\pm$ SD below each graph. * $p < 0.05$ by the Friedman test. Post hoc test: † $p < 0.05$ between after TAVI and 6 months.

Table 2

Baseline clinical and echocardiographic characteristics in patients with and without significant aortic regurgitation post-transcatheter aortic valve implantation

Variable	Aortic Regurgitation		p-value*
	≥ 2 (n=47)	< 2 (n=128)	
Age (years)	81.3 $\pm$ 5.4	80.5 $\pm$ 6.9	0.43
Men	21 (45%)	43 (34%)	0.22
Body surface area (m ²)	1.75 $\pm$ 0.22	1.73 $\pm$ 0.19	0.62
Logistic EuroSCORE (%)	22.5 $\pm$ 12.8	19.7 $\pm$ 10.6	0.62
NYHA functional class			0.24
II	8 (17%)	34 (27%)	
III	25 (53%)	69 (54%)	
IV	14 (30%)	25 (19%)	
Previous myocardial infarction	11 (23%)	25 (20%)	0.64
Previous coronary bypass surgery	8 (17%)	29 (23%)	0.53
Previous percutaneous coronary intervention	13 (28%)	34 (23%)	1.00
Peripheral vascular disease	16 (34%)	53 (41%)	0.49
Hypertension	38 (81%)	100 (78%)	0.84
Hypercholesterolaemia	22 (47%)	62 (48%)	0.87
Diabetes mellitus	14 (29%)	30 (23%)	0.43
Hemoglobin (g/dL)	12.0 $\pm$ 1.3	12.1 $\pm$ 1.7	0.60
Aortic valve area (cm ²)	0.70 $\pm$ 0.15	0.70 $\pm$ 0.17	0.22
Mean transaortic gradient (mmHg)	48 $\pm$ 17	48 $\pm$ 16	0.91
Aortic annulus (cm)	22.0 $\pm$ 1.8	21.6 $\pm$ 1.9	0.17
Left ventricular end-diastolic volume index (ml/m ²)	69 $\pm$ 29	62 $\pm$ 20	0.25
Left ventricular end-systolic volume index (ml/m ²)	34 $\pm$ 24	29 $\pm$ 18	0.20
Left ventricular ejection fraction (%)	53 $\pm$ 12	56 $\pm$ 13	0.25
Left ventricular mass index (g/m ²)	163 $\pm$ 55	144 $\pm$ 37	0.03
Left atrial volume index (ml/m ²)	57 $\pm$ 17	51 $\pm$ 19	0.11
Aortic regurgitation pre-TAVI	Grade 0-1 33 (70%)	93 (73%)	0.85
Grade 2-3 14 (30%)	35 (27%)		
Prosthesis size	23 mm 19 (40%)	51 (40%)	1.00
26 mm 28 (60%)	77 (60%)		

Continuous data are presented as mean $\pm$ SD and categorical data as n (%). * p value for comparison between aortic regurgitation ≥ 2 and < 2 using unpaired t test or chi-square test.

patients (76%). AR was classified as none in 77 (25%), grade 1 in 155 (49%), and grade 2 in 81 patients (26%). Only 1 patient (0.3%) had moderate-to-severe AR (grade 3) at the end of the procedure despite reballoning. Significant AR after TAVI, defined as AR grade ≥ 2 , was observed in 82 patients (26%). Over a mean follow-up of 19 months (median 18, 25th to 75th percentile 10 to 28), the overall survival rates at 6 months, 1 year, and 2 years were 96%, 92%, and 84%, respectively. There were a total of 43 deaths: 18 (22%) in patients with post-TAVI AR grade ≥ 2 and 25 (11%) in patients with post-TAVI AR grade < 2 . Importantly, there was a trend toward a reduced survival in patients with post-TAVI AR grade ≥ 2 compared with patients without significant AR, at 1 year (93% vs 91%) and at 2 years (89% vs 74%, log-rank $p = 0.06$; Figure 1).

To evaluate the changes over time of AR after TAVI, complete echocardiographic data were available in 175 patients who survived at least 12 months. Post-TAVI AR was present in the majority ($n = 136$, 78%). The overall AR was considered grade 1 in 89 (51%) and grade 2 in 47 patients (27%). In the presence of post-TAVI AR, paravalvular AR was the most common (83%), whereas intravalvular AR was less frequent (42%), with 25% of patients having both AR. The evolution of overall, paravalvular, and intravalvular AR severity was compared before discharge, at 6 months, and ≥ 12 months after TAVI. No significant change in the overall AR was observed over time (Friedman $p = 0.37$; Figure 2). Of note, paravalvular AR appeared to improve (Friedman $p = 0.014$; Figure 2), whereas intravalvular AR was unchanged over time (Friedman $p = 0.95$; Figure 2).

When the population was analyzed according to the presence or absence of significant post-TAVI AR, marked improvement in the overall AR was observed in patients with overall AR grade ≥ 2 ($n = 47$, Friedman $p < 0.001$) with a significant change noted between after TAVI and at 6 months, which was stable over time (Figure 2). In contrast, patients with overall AR grade < 2 ($n = 128$) did not show any change over time (Figure 2). Concerning paravalvular

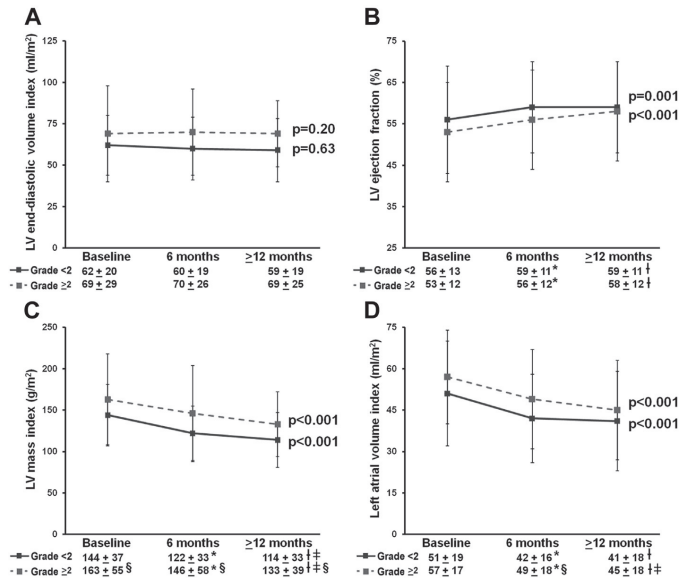


Figure 3. Comparison of changes in LV end-diastolic volume index (A), LV ejection fraction (B), LV mass index (C), and left atrial volume index (D) in patients with (grade ≥ 2) and without (grade < 2) significant post-TAVI AR. Measurement values (mean $\pm$ SD) at the corresponding time point are given below each graph. p Value by repeated measures of variance. Bonferroni post hoc test: *p < 0.05 between baseline and 6 months. †p < 0.05 between baseline and ≥ 12 months. ‡p < 0.05 between 6 and ≥ 12 months. §p < 0.05 between AR grade < 2 and ≥ 2 .

AR, no significant change in paravalvular AR was observed over time in patients with post-TAVI paravalvular AR grade < 2 (n = 143). Importantly, in patients with post-TAVI paravalvular AR grade ≥ 2 (n = 32), significant improvement in paravalvular AR was observed (Friedman p = 0.002), particularly during the first 6 months (Figure 2). Concerning intravalvular AR, most patients had no significant intravalvular AR (n = 167), whereas significant intravalvular AR was present in only 8 patients. Of note, intravalvular AR remained stable, with no significant changes observed over time, regardless of intravalvular AR grade ≥ 2 or < 2 (Figure 2). In terms of absolute number of patients, worsening in post-TAVI AR from AR grade < 2 to ≥ 2 over time was uncommon (n = 7, 4%). Only 4 patients with mild paravalvular AR developed moderate AR at 6 months, which remained stable thereafter. Among the 3 patients with mild intravalvular AR, 2 patients progressed to moderate AR, while 1 patient developed severe intravalvular AR (from endocarditis) by 6 months. In patients with post-TAVI paravalvular AR grade ≥ 2 (n = 32), notably 9 patients (28%) had reduction in AR to none or mild AR, while only 1 patient (3%) developed severe AR because of endocarditis at 6 months. In contrast, among those with post-TAVI intravalvular AR grade ≥ 2 (n = 8), AR remained unchanged in the majority (n = 7, 88%), and 1 patient (1%) developed severe AR by 6 months, requiring surgery.

To evaluate the hemodynamic effect of significant post-TAVI AR in the subgroup of 175 patients, the echocardiographic variables at 6 and ≥ 12 months were compared.

Table 2 summarizes the baseline clinical and echocardiographic characteristics of patients with post-TAVI AR grade ≥ 2 (n = 47) and AR grade < 2 (n = 128). During follow-up, no significant changes in LV end-diastolic volumes were observed in both groups (Figure 3). Importantly, patients with post-TAVI AR grade ≥ 2 did not exhibit a significant increase in LV end-diastolic volume over time. Of note, a significant improvement in LV ejection fraction was observed in both groups (Figure 3). Although patients with post-TAVI AR grade ≥ 2 had a larger LV mass at baseline, both groups showed significant LV mass regression over time. In fact, LV mass regression was noted at 6 months and continued to regress beyond 12 months (Figure 3). Similar reduction in LA volume was also observed in both groups over time (Figure 3). In terms of transvalvular hemodynamics, significant improvement in mean gradient and aortic valve area was noted at 6 months for patients with AR grade ≥ 2 (48 ± 17 vs 12 ± 7 mm Hg and 0.70 ± 0.15 vs 2.09 ± 0.53 cm²) and with AR grade < 2 (48 ± 16 vs 11 ± 4 mm Hg and 0.70 ± 0.17 vs 1.97 ± 0.43 cm²), respectively. The majority of patients (n = 166, 95%) reported an improvement in New York Heart Association functional class by ≥ 1 class, compared with baseline. However, 6 patients (13%) with post-TAVI AR grade ≥ 2 (n = 47) compared with only 3 patients (2%) with post-TAVI AR grade < 2 (n = 128) reported no improvement in functional class.

Given that significant changes in AR occurred within 6 months after TAVI, the effect of significant AR at 6 months on survival was further examined in this group (n = 175).

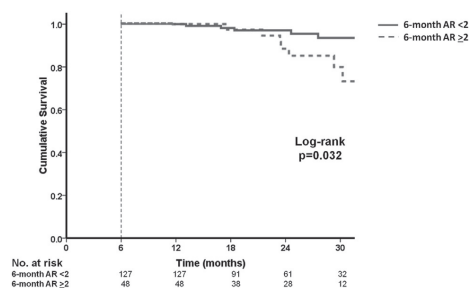


Figure 4. Survival Kaplan-Meier curves for patients with 6-month AR ≥ 2 or AR < 2 after TAVI.

Forty-eight patients (27%) had significant 6-month AR grade ≥ 2 . Over a mean follow-up of 25 months (median 24, 25th to 75th percentile 18 to 30), more deaths were observed in patients with 6-month AR grade ≥ 2 ($n = 7$, 15%) than in patients with 6-month AR grade < 2 ($n = 5$, 4%). A significant reduction in survival was noted in patients with 6-month AR grade ≥ 2 compared with those without significant 6-month AR ($n = 127$) at 1 year (97% vs 98%) and at 2 years (80% vs 94%, log-rank $p = 0.032$; Figure 4).

Discussion

The present study showed that significant AR is common immediately after TAVI and that patients with AR grade ≥ 2 tended to have a less favorable clinical outcome. However, significant AR after TAVI, and in particular paravalvular AR, appeared to improve during the first 6 months after implantation. Interestingly, improvement in LV ejection fraction, together with LV mass regression and LA volume reduction, was similar among patients with and without AR grade ≥ 2 . Nevertheless, patients who remained with AR grade ≥ 2 at 6-month follow-up showed significantly worse survival than patients with AR grade < 2 .

Trivial or mild AR, particularly paravalvular, is common and often an acceptable finding after TAVI because of incomplete annular sealing of the transcatheter valve within a calcified aortic valve.^{3,4} Recently, there is a growing interest in the effect of AR on outcomes after TAVI.^{2,5,6} In their series, Abdel-Wahab et al⁵ showed that patients with AR grade ≥ 2 had a significantly higher in-hospital mortality than those with no or mild AR after TAVI. Because early in-hospital mortality is mainly determined by procedural complications,² the present study, therefore, focused on patients who survived the TAVI procedures and examined the midterm all-cause mortality associated with AR. A strong trend toward reduced survival among patients with post-TAVI AR grade ≥ 2 was observed. This is consistent with recent studies that identified presence of moderate or severe post-TAVI AR as an independent predictor of survival at 1 year.^{2,6} The Placement of Aortic Transcatheter Valves A trial further confirmed that the effect on mortality at 2 years was proportional to post-TAVI AR severity, even when AR was only mild.⁴ These observations underscore the importance of reducing AR to a minimum after TAVI.

Currently, it is still unclear how post-TAVI AR evolves over time. This study observed that paravalvular AR appeared to diminish in severity over time. Importantly, significant paravalvular AR (grade ≥ 2) after TAVI appeared to improve, particularly within the first 6 months. In a 3-year follow-up study with balloon-expandable valves, patients with moderate AR after TAVI reported improvement to mild AR or remained unchanged by 6 months, although the components of AR were not described.¹⁶ A possible explanation for the progressive reduction in paravalvular AR after balloon-expandable valve implantation is the presence of positive remodeling of the aortic annulus.¹⁷ Over time, the stented prosthesis may adapt to better accommodate and seal the calcified native commissures and thus, minimizing the paravalvular leak.

There are limited data regarding the effect of AR on cardiac performance after TAVI. Although significant AR after TAVI is associated with worse clinical outcomes,^{2,5,6} the direct causal relation between AR and mortality remains to be determined, and it is unclear if this is mediated by its hemodynamic consequences on the LV or by other mechanisms associated with noncardiovascular events.¹⁸ In patients with severe AS, the stiff and hypertrophied LV has adapted to the long-standing pressure overload state and is associated with impaired relaxation and elevated LV end-diastolic pressure.¹⁹ Accordingly, when AR develops after TAVI, there is a concern that the AR volume may precipitate a further increase in the already elevated LV end-diastolic pressure, resulting in acute pulmonary edema or inducing LV dilatation in the midterm. This study confirmed that LV ejection fraction improved, accompanied by LV mass regression in both groups of patients (AR grade ≥ 2 and < 2) after TAVI. Interestingly, LV volumes did not increase over time in patients with significant AR, suggesting that the derived hemodynamic benefit of TAVI after the relief of AS still outweighed the perceived negative effect of AR after TAVI, at least at midterm follow-up. In a 5-year follow-up of 84 patients with surgical aortic valve, Rallidis et al²⁰ also reported that LV dimensions did not differ in patients with or without paravalvular leak, whereas the wall thickness decreased and fractional shortening increased in both groups.

Although significant AR was not associated with overt harmful effect on LV structure and function on echocardiography, its undesirable effects on clinical outcomes should not be overlooked. More patients with significant post-TAVI AR reported no improvement in functional class, compared with patients with AR grade < 2 in this study, which is consistent with the study by Gotzmann et al,²¹ that identified moderate and severe AR as an independent predictor of no improvement of functional class at 6 months. Moreover, the present study highlighted that patients with significant AR that persisted at 6 months were also associated with worse survival (Figure 4). In comparison with previous studies that focused on post-procedural AR and its negative effect on early survival,^{2,4-6} this study observed the negative association between significant AR at 6 months after TAVI and late survival. Other mechanisms that are beyond the scope of this study may be responsible for the poor outcomes, such as undesirable neurohumoral changes, impaired coronary flow, and possible higher risk of hemolysis.

We acknowledge that inclusion of only patients who survived at least 12 months may have limited the ability to

draw definite conclusion. However, the aim of the study was to examine how AR after TAVI changes over time, and this could only be studied in patients who survived a period of time after the procedure and underwent systematic echocardiographic examination. Moreover, transthoracic Doppler echocardiography only provides a semiquantitative hemodynamic assessment of AR severity and is subjected to variability and requires further validation.

Disclosures

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